SKIN

IN-DEPTH REVIEW

Off-Label Uses of Upadacitinib

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ABSTRACT

Background: Janus Kinase (JAK) inhibitors interfere with the JAK-STAT signaling pathway, which is vital in regulating inflammation and immune function. Notably, upadacitinib, a JAK inhibitor, has been increasingly used as a treatment modality for refractory inflammatory diseases.
Methods: A literature review was conducted on Pubmed and Clinical Trials.gov using the keywords “upadacitinib” combined with “off-label”, “dermatology”, “skin”, or “cutaneous” from October 1st, 2021, to October 1st, 2023. 941 articles were reviewed, and 50 articles were included.
Results: The systematic search revealed 20 different dermatology conditions treated with off-label use of upadacitinib. Most of these conditions showed drastic improvement by actively decreasing the inflammatory response involved in their pathogenesis. The most common side effects reported for the medication were elevated creatine kinase, headaches, urinary tract infections, and acne. Patients should also be advised to consider the shingles vaccines prior to upadacitinib treatment.
Conclusion: Upadacitinib shows potential utility in treating refractory inflammatory dermatologic conditions, treatment-resistant pruritus, and medication-induced skin reactions. Further large-scale, controlled clinical trials are needed to evaluate the further indications of upadacitinib and its safety profile.

INTRODUCTION

According to Google Trends, in January of 2023, the words “Janus kinase inhibitor” had a 29-point value for search activity on Google. On June 15, 2023, the point value increased to 100. The first JAK inhibitor, ruxolitinib, was FDA-approved in 2011, and now there are a total of nine approved JAK inhibitors for the treatment of rheumatologic, dermatologic, gastrointestinal, neoplastic indications, and COVID-19.[1] The first used JAK inhibitor was tofacitinib in 2012 to treat adult patients with rheumatoid arthritis.[2] Due to their unique safety and efficacy profiles, the use of JAK inhibitors for various dermatologic indications is rapidly growing.[3] Janus kinase inhibitors (JAKi) block the JAK-STAT signaling pathway.[3] This signaling pathway is essential for proper immune function, and inhibition will lead to decreased production of certain inflammatory cytokines.[3,4] The JAK protein family consists

of JAK1, JAK2, JAK3, and TYK2.[4] These enzymes normally promote inflammation and are involved in several diseases.[4] By interfering with the signaling pathways, JAK inhibitors can be used as treatments for inflammatory disease.[4]

Upadacitinib works by blocking Janus Kinase, specifically JAK 1, more than others, reducing off-target JAK inhibition and side effects.[5] It is approved for the treatment of atopic dermatitis (AD) (≥ 12 years), rheumatoid arthritis (RA), psoriatic arthritis (PsA), ankylosing spondylitis (AS), non-radiographic axial spondylarthritis, ulcerative colitis (UC), and Crohn's disease (CD).[6]
This review article highlights all the off-label dermatologic uses of upadacitinib to date.

METHODS

A systematic literature search was performed and conducted on Pubmed and Clinical Trials.gov, including case reports, clinical trials, case series, cohort studies, and clinical letters from October 1st, 2021 to October 1st, 2023. The keywords in the advanced search were "upadacitinib" in combination with "off-label", "dermatology", "skin", or "cutaneous". Once a condition was found to be treated with upadacitinib, a supplemental electronic search in that database with the advanced search of "upadacitinib" and the specific dermatologic disorder was conducted. The articles included were not limited by the type of study. A total of 941 articles were reviewed, of which 50 were included.

RESULTS

The systematic search revealed 20 different dermatology conditions treated with Upadacitinib [**Table 1, Supplementary Table 1**]. Many dermatological skin conditions improved with upadacitinib; particularly, refractory cases appeared to respond well to upadacitinib therapy.

Alopecia Areata (AA)

JAK inhibitors, such as ritlecitinib and baracitinib, have been approved for the treatment of alopecia areata.[7,8] Although upadacitinib has not been approved for the condition, it has shown promising results in multiple patients. Multiple case reports and case series with patients presenting with near-to-complete hair loss refractory to conventional treatments have shown complete scalp regrowth within months of treatment.[9–14] Moreover, upadacitinib has been shown to help five patients with alopecia universalis, helping hair regrowth not only on their scalp but on other areas as well.[15–19] One retrospective cohort study showed a 90% improvement in the Severity Alopecia Tool (SALT) score after 24 weeks of treatment.[20] In addition, upadacitinib successfully treated adalimumab-induced alopecia areata in a patient with Crohn's disease.[18] Interestingly, another patient was treated for only three months and presented four months later with a SALT score of 0.[21]

There is currently an ongoing clinical trial investigating the clinical efficacy of upadacitinib for alopecia areata (NCT06012240).[22]

Psoriasis (PsO)

Although upadacitinib is approved for the treatment of psoriatic arthritis, it is not approved for psoriasis. A little more than half of the study participants in a phase 3 trial for psoriatic arthritis reached a 75% reduction in baseline Psoriasis Area and Severity Index (PASI).[23,24] Other studies have shown improvement in palmoplantar psoriasis and

severe nail psoriasis with 15 mg upadacitinib.[25,26] Upadacitinib also led to

Table 1. Reported Off-Label Uses of Upadacitinib

Skin/Dermatologic Condition	# of articles/papers	# of reported patients
Alopecia Areata	13	57
Psoriasis	6	218
Palmoplantar Pustulosis	3	9
Hidradenitis Suppurativa	3	68
Erythema Multiforme	3	3
Granuloma Annulare	2	2
Lichen Planus	2	2
Pyoderma Gangrenosum	2	2
Pityriasis Rubra Pilaris	2	2
Vitiligo	2	13
Bullous Pemphigoid	2	2
Chronic Prurigo	2	4
Pemphigus foliaceus	1	1
Lichen Amyloidosis	1	1
Netherton Syndrome	1	1
Chronic Pruritus	1	1
Erythrodermic mycosis fungoides	1	1
Hailey Hailey Disease	1	1
Acne Keloidalis Nuchae	1	1
Epidermolysis bullosa pruriginosa	1	1

improvement in drug-induced psoriasiform dermatitis (n=2) after the responsible medications (dupilumab and adalimumab) were discontinued and topical and systemic steroids failed to improve the skin.[27,28]

Palmoplantar Pustulosis

The treatment of refractory palmoplantar pustulosis can be challenging. Upadacitinib has shown some clinical efficacy in the clearance of lesions while minimizing pruritus and pain. One case series showed a reduction in the severity of the palmoplantar pustulosis from moderate and severe (Palmoplantar Pustulosis Physician Global Assessment [PPPGA] 3-4) to almost clear and clear (PPPGA 0-1) and resolution of itch in all three patients.[29] Similarly, another case series (n=5) and case report demonstrated an improvement in their Palmoplantar Pustulosis Area and Severity Index (PPPASI) at variable times (6-15 weeks).[30,31] Patients with a history of psoriatic arthritis showed improvement in their joint pain, and interestingly, one patient with chronic spontaneous urticaria (CSU) showed improvement, and omalizumab could be discontinued.[30]

Hidradenitis Suppurativa (HS)

In a phase 2, placebo-controlled trial, 38.3% of participants (n=47) with moderate-severe HS treated with 30 mg upadacitinib showed a more than or equal to 50% reduction in abscess and nodule count (Hidradenitis Suppurative Clinical Response [HiSCR] 50)

after twelve weeks of treatment.[32,33,34] In a retrospective study, upadacitinib treatment resulted in HiSCR 75 in 19/20 patients.[35] Reported side effects included transient transaminitis, elevated creatine kinase, covid-19 infections, urinary tract infections, headaches, acne, and cellulitis.[35] In addition, one patient experienced varicella zoster infection, and another was found to have prostate cancer.[35] Similarly, one case report of an HS patient treated with upadacitinib for five weeks developed a varicella zoster infection.[36] However, their presentation was exacerbated and complicated by sepsis, encephalitis, pneumonia, and haemophagocytic lymphohistiocytosis.[36]

There is currently one clinical trial enrolling moderate to severe HS patients who have previously failed TNF blockers (NCT05889182).[37]

Erythema Multiforme (EM)

Treatment for resistant erythema multiforme (EM) may be complicated. Upadacitinib was started for three patients with EM, which resulted in the clearance of most skin lesions.[38–40] One of the patients was started on upadacitinib after EM worsened months after being actively controlled by tofacitinib; however, with upadacitinib, their EM remained close to remission even during long-term follow-up.[38]

Granuloma Annulare (GA)

There have been two reported cases in which upadacitinib cleared granuloma annulare.[41,42] One patient with diffuse GA was being treated for rheumatoid arthritis, while the other patient's GA was more localized to the thighs. [41,42] Both patients' skin cleared within four months of starting treatment.[41,42]

Lichen Planus

There have been two cases showing complete resolution of oral erosive lichen planus with the treatment of upadacitinib with variable timing (1-24 weeks).[43,44] However, one patient not only showed improvement in her oropharynx, esophageal pain, and dysphagia, but also a significant reduction in the lymphocytic infiltrate in the esophageal mucosa after 12 weeks of treatment.[44]

Pyoderma Gangrenosum (PG)

Pyoderma gangrenosum can often be seen as a manifestation of inflammatory bowel and rheumatologic diseases. To date, there are two case reports showing successful treatment of PG with upadacitinib: one patient with a history of treatment-resistant HLA-B27 negative spondylarthritis and the other with rheumatoid arthritis (RA).[45,46] The treatment course of the patient with spondylarthritis was complicated by PG-induced ulcers and cryptogenic organizing pneumonia from TNF-alpha inhibitors and demonstrated complete remission after 12 weeks of treatment with 15 mg of upadacitinib and prednisone.[45] Similarly, the other patient with RA-associated PG showed decreased activity and size with resolution of inflammatory markers and cessation of pain after 14 weeks.[46]

Pityriasis Rubra Pilaris (PRP)

There have been two case reports reporting improvement of PRP with upadacitinib treatment after failing conventional treatments. One patient with a significant cardiovascular history presented with pruritic generalized erythroderma without the involvement of thighs and hands and demonstrated significant improvement after four weeks of 15 mg upadacitinib initiation with a body surface area (BSA) of less than

1%, improved pruritus, and complete scalp hair regrowth.[47] The other patient presented with diffuse salmon-colored patches (BSA 80%) that were partially responsive, demonstrating a 25% BSA improvement after two weeks and a 65% improvement after increasing to 30 mg upadacitinib after six weeks.[48]

Vitiligo

JAK inhibitors have been shown to have great efficacy in the treatment of non-segmental vitiligo. Upadacitinib has been shown to increase re-pigmentation in patients with vitiligo (n=12) and improve the Vitiligo Area Severity Index on average by 38.6% and with higher percentages for the face (51.4%).[49] Similarly, another case reported 90% repigmentation on the patient's face after four months of treatment.[50] A clinical trial investigating the treatment of upadacitinib for vitiligo has been completed (08/2023); however, results have not been released yet (NCT04927975).[51]

Bullous Pemphigoid (BP)

There have been two cases reporting the use of upadacitinib for bullous pemphigoid. In both patients, there was decreased active bulla formation, and one of the patients was successfully treated with significant improvement in their blistering plaques and bullae with only residual post-inflammatory hyperpigmentation after five months of treatment.[52,53] The other patient had a significant malignancy history with active metastatic cancer (PD-L1 tumor) and experienced drug-induced bullous pemphigoid from the immunotherapy (MK-4830 in combination with pembrolizumab).[53] Although the patient was already receiving end-of-life care before the initiation of upadacitinib, he or she did show improvement in his or her urticaria and BP before passing away two months after upadacitinib initiation.[53]

Chronic Prurigo

Gil-Lianes et al. reported three patients with treatment-resistant chronic prurigo demonstrating resolved pruritus after two weeks of treatment with upadacitinib and clearance of cutaneous lesions with some residual hyperpigmentation after 1-2 months.[54] Moreover, 30 mg upadacitinib successfully cleared all prurigo nodularis lesions except one, and eventually, there was only post-inflammatory hyperpigmentation present in previous areas after 16 weeks of treatment.[55]

Pemphigus Foliaceous

A patient with pemphigus foliaceous was treated with upadacitinib after a lack of improvement of topical corticosteroids and prednisone.[56] The patient later had no active bullae and continued treatment led to improvement of previous bullae and patches and eventual clearance with only post-inflammatory hyperpigmentation in affected areas.[56]

Lichen Amyloidosis

One patient with cutaneous lichen amyloidosis showed significant improvement in pruritus and pain with slight flattening of papules.[57]

Netherton Syndrome

There has been one case report of a patient with widespread Netherton Syndrome that demonstrated initial improvement with a 24% decrease in BSA.[58] However, her skin worsened after the next few months.[58]

Chronic Pruritus

One case report described the resolution of longstanding pruritus secondary to polycythemia vera after six months of upadacitinib.[59] However, she experienced the formation of painful facial acneiform lesions that were later managed with topical ivermectin.[59] Some of her previous therapies improved her itch but had other side effects, such as gabapentin (drowsiness), while other therapies improved itch transiently (dupilumab).[59]

Erythrodermic Mycosis Fungoides

15 mg upadacitinib decreased widespread erythematous patches and scale from BSA of more than 80% to less than 10% after 16 weeks and improved pruritus.[60]

Hailey-Hailey Disease

Murphy et. al reported that upadacitinib cleared all generalized plaques of a patient with Hailey-Hailey disease after four weeks of Upadacitinib treatment.[61]

Acne Keloidalis Nuchae

One patient with acne keloidalis nuchae showed drastic improvement in erythema and crust with 10 months of treatment.[62]

Epidermolysis Bullosa Pruriginosa

Kim et. al. reported significant improvement in pruritus with no active new bullae in a patient with epidermolysis bullosa pruriginosa after 10 weeks of treatment with upadactinib.[63]

DISCUSSION

The JAK/STAT pathway is one of the main signaling cascades that lead to the upregulation of cytokines that mediate inflammatory conditions.[64] Upadacitinib, a JAK1 inhibitor, prevents the activation of STAT proteins, leading to the downregulation of pro-inflammatory downstream targets involved in the cutaneous manifestation of disease.[64] The improvement seen in 20 different dermatology conditions may be related to the JAK/STAT pathway and reduced production of specific cytokines leading to the progression of the disease (displayed in **Table 2**).

The results with upadacitinib for some of these conditions have been very promising and have led to the development of clinical trials to investigate the effects in larger sample sizes (alopecia areata, vitiligo, and hidradenitis suppurativa). Of note, many patients treated with off-label upadacitinib in this review also had concomitant treatment-resistant pruritus (21 patients), in some cases with concomitant atopic dermatitis (11 patients) and previous treatments of dupilumab (7 patients). Pruritus resolved with the improvement of the primary condition. Upadacitinib inhibits IL-4 and IL-31, important activators in afferent sensory nerves and T-cell-dependent itch, suggesting a role in managing treatment-resistant pruritus.[57] Upadacitinib may have some clinical utility in managing treatment-resistant pruritus.

Although upadacitinib has shown great results in these patients and may benefit other patients with inflammatory conditions, patients should be screened and monitored according to appropriate guidelines. Patients should be monitored for adverse side effects (upper respiratory infections, elevated liver enzymes) and their respective black box warnings (opportunistic infections, malignancies, thrombosis, cardiovascular events, mortality).[64] The most common adverse effects reported with off-label use were elevated creatine kinase (n=16), acne

formation (n=11), headaches (n=10), UTI (n=6), opportunistic infections (VZV n=2, Herpes simplex n=1), upper respiratory infection (n=4), mild transaminitis (n=3),

Table 2. Reported Mechanism (Cytokines)/Pathway involved in Off-label Dermatology Conditions treated with Upadacitinib.

Skin/Dermatologic Condition	Cytokine/Pathway Downregulation
Alopecia Areata	IL-4[13], Th2 cells, IFN-gamma, IL-15[19]
Psoriasis	JAK1, JAK/STAT[25]
Palmoplantar Pustulosis	Not clear[29], JAK/STAT
Hidradenitis Suppurativa	JAK/STAT[32]
Erythema Multiforme	IFN-gamma, IL-15[65]
Granuloma Annulare	Th2, JAK/STAT[41]
Lichen Planus	JAK1, IFN-gamma, IL-21[44]
Pyoderma Gangrenosum	pJAK1 overexpressed[46]
Pityriasis Rubra Pilaris	IL-17/IL-23[48]
Vitiligo	IFN-gamma[49]
Bullous Pemphigoid	JAK/STAT, Th2, IL-4, IL-13[52]
Pemphigus foliaceus	IL-4, Th2[56]
Lichen Amyloidosis	T cells, IL-31, IL-4[57]
Netherton Syndrome	Th2, IL-4, IL-5[58]
Chronic Prurigo	IL-31[54], JAK/STAT[55]
Chronic Pruritus	JAK /STAT
Erythrodermic mycosis fungoides	JAK/STAT
Hailey-Hailey Disease	Th2, IL-4, IL-13[61]
Acne Keloidalis Nuchae	JAK/STAT
Epidermolysis bullosa pruriginosa	JAK/STAT

laboratory abnormalities (n=3), nausea (n=2), and pulmonary infection (n=2). There was one patient who died on upadacitinib; however, that patient already had metastatic cancer prior to the initiation of upadacitinib.[53] Another patient was found to have prostate cancer during the hidradenitis suppurativa clinical trial.[35]

There have also been a few reports of upadacitinib causing secondary dermatology conditions: Kaposi Sarcoma in a patient with rheumatoid arthritis and generalized pustular psoriasis (GPP) in a patient with unspecified arthritis.[66,67] JAK inhibitor-induced Kaposi sarcoma has been previously reported; however, the patient's Kaposi sarcoma resolved after discontinuing upadacitinib after seven months without treatment presented with post-inflammatory hyperpigmentation in previously affected areas and worsening arthritis.[66] The other patient developed GPP after temporarily stopping upadacitinib and methotrexate for two weeks due to a persistent cough, and GPP resolved after restarting treatment and etretinate.[67]

Although it is not a contraindication for upadacitinib, it is worth mentioning that there were two patients with significant cardiovascular histories (atrial fibrillation, hypertension, aortic valve repair, coronary artery disease s/p CABG, and hyperlipidemia) that, except for some laboratory abnormalities (transient elevation of lipase/amylase), experienced no adverse side effects.[16,47]

CONCLUSION

Overall, upadacitinib has a lot of potential clinical utility with other future applications, including treatment-resistant pruritus, inflammatory skin conditions, and medication-induced skin reactions. However, there is limited research on these off-label uses as most studies were case reports. Further research with larger sample sizes is needed to investigate clinical efficacy and safety.

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Supplementary Table 1. Identified Studies of the Off-Label Use of Upadacitinib for the treatment of Dermatology Conditions.

Disease	Author	Daily Dose	Type of Evidence	# of Individuals Treated	Comorbidities (patient # if applicable)	Previous Treatments	Before Initiation	Outcome	Adverse Events Reported
Alopecia Areata	Flora et. Al., 2023	15 mg-30 mg QD UPA	Retrospective cohort study	25	atopic dermatitis (4 patients)	n/a	Median of SALT-50, DLQI 15	SALT 5 (24 weeks), DLQI 2 (24 weeks)	Nausea (two patients), headache (1 patient), resolved after 4 weeks
	Chiricozzi et. Al., 2023	30 mg QD UPA	Retrospective study	19	Graves disease (1), Hashimoto Thyroiditis (4), Autoimmune gastritis (1), Asthma (6), Rhinitis (5)	Cyclosporine (12), oral corticosteroids (4), azathioprine (1), dupilumab (8)	Mean SALT-95.1 (19 patients)	Mean SALT-31.0 (Week 28 for 14 patients)	Increased ALT and homocysteine blood levels (1 patient), leukocyte count (2 patients) then reduced to 15 mg
	Kołcz et. Al., 2023	15 mg	Case Report	1	atopic dermatitis	Topical 5%minoxidil, mometasone fumarate, diphenylcyclop	SALT-100	SALT 0 (12 weeks); complete resolution of AD	None

						ropenone, NBUVB			
	Novielli et Al., 2023	15 mg-30 mg QD UPA	Case Report	1	atopic dermatitis, Crohn's, ileal subocclusion s/p ileal resection	Topical corticosteroids, cyclosporine, azathioprine, dupilumab, infliximab, adalimumab, ustekinumab	SALT-100	EASI 1 SALT 0 (1 month); Stool Bristol Scale, frequency, abdominal pain improved (3 months); Colonoscopy normal (9 months)	Acneiform facial eruptions (30 mg)
	Bourkas et. Al., 2022	Not available UPA	Case report	1	atopic dermatitis, allergenic rhinitis, asthma	Intralesional corticosteroid injections, topical corticosteroids, 0.1% tacrolimus cream, folic acid supplementation, methotrexate, cyclosporine, oral minoxidil, spironolactone	SALT*-90	SALT 0 (5 months)	None
	Walls et. Al., 2023	15 mg QD UPA	Case report	1	atopic dermatitis	Methotrexate, oral corticosteroids,	EASI-18, IGA-4,SALT-75	EASI 0 (1 month);	None

						topical corticosteroids, topical tacrolimus, cyclosporin, dupilumab,		SALT 0 (4 months)	
	Johnston et. Al., 2023	30 mg QD UPA	Case report	1	Crohn's disease	Intralesional triamcinolone acetonide injection, adalimumab, ustekinumab, systemic corticosteroids, methotrexate	SALT-100	SALT 0 (7 months); CD in clinical remission	None
	Yu et. Al., 2023	15 mg QD UPA	Case report	1	atopic dermatitis	Topical steroids, minoxidil, tacrolimus, glycyrrhizin tablets, glucocorticoids	SALT-98, EASI 2.5	SALT-9 (5 months); AD complete remission	None
	Asfour L et. Al., 2022	Not available	Case report	1	atopic dermatitis	Baracitinib	EASI-37.4, DLQI 12, SALT-6	Eczema clear; DLQI 2; regrowth in AA in preauricular areas and partially eyebrows (4 weeks)	None

	Yousse f et Al., 2023	15 mg QD UPA	Case Report	1	hypertension, hyperlipidemi a, coronary artery disease s/p CABG	Intralesional and oral steroids	SALT 100	SALT 0; normal nails	Transient elevated serum lipase and amylase later resolved
	Cantelli et. Al., 2022	30 mg QD UPA	Case Report	1	atopic dermatitis	Topical and systemic corticosteroids, cyclosporine, dupilumab	EASI -45.1, P-NRS 8/10, SALT-91.5	Regrowth of hair all over scalp (3 months); improved AD	None
	Gori et. Al., 2023	30 mg QD UPA	Case report	1	none	Topical diphencyprone, intramuscular triamcinolone, oral cyclosporine, methotrexate	SALT-100	SALT-9 (12 weeks)	None
	Johnsto n et. Al.,202 3	30 mg QD UPA	Case Series	3	(2) Atopic Dermatitis; (3) Atopic Dermatitis, Liver Cirrhosis	(1) diphenylcyclop ropenone, prednisone, minoxidil solution, intralesional triamcinolone acetonide, squaric acid dibutyl ester, methotrexate, topical	(1-2) Patches of hair loss in multiple areas of scalp (3) SALT-90	(1) SALT 0 (8 months); (2) Discontinue d at 3 months but showed SALT-0 (7 months), AD cleared; (3) SALT-0 (4 months) AD cleared	Mild acne (1 patient)

						tofacitinib, bimatoprost eye drops, (2) Topical tofacitinib, bimatoprost eye drops, intralesional triamcinolone acetonide, (3) prednisone			
Psoriasis	Gargiulo et. Al., 2023	15 mg QD UPA	Case Series	3	(1) atopic dermatitis (2) allergies to several inhalants, atopic dermatitis (3) psoriatic spondyloarthropathy (4) atopic dermatitis	(1) Ustekinumab, dupilumab, (2) Cyclosporin, brodalumab, (3) Salazopyrin, methotrexate, ustekinumab, secukinumab, apremilast, (4) Acitretin, methotrexate, adalimumab, risankizumab, dupilumab	(1) PASI 10, DLQI >10, PsO on back, shoulder, onychopathy, genitals, soles (2) i-NRS (9/10), DLQI 15, PsO elbows, palms, pubic region (3) i-NRS 10/10, pain-VAS 80/100,palmoplantar PsO (4) Palmoplantar PsO on soles and	(1) Complete resolution of AD and PsO: PASI 0 (16 weeks), (2) PsO skin clearance (16 weeks), (3) Symptoms improved (4 weeks), (4) PsO skin clearance (16 weeks), resolved pruritus	None

							lower extremities		
	Mease et. Al., 2021	15 mg QD UPA	Phase 3 Clinical Trial	211	N/A	N/A	N/A	52.3%/40.8%/26.9% of patients achieved PASI 75/90/100	N/A
	Wang et. Al., 2023	15 mg QP UPA	Case Report	1	none	Oral Chinese medicine, topical corticosteroids,	Severe nail psoriasis: NAPSI 80, DLQI 20	NAPSI 15, DLQI 10 (week 16); NAPSI 6 (Week 20)	None
	Martinez-Molina et. Al., 2023	15 mg QD UPA	Case Report	1	psoriatic arthritis	PUVA therapy, cyclosporin, azathioprine, ustekinumab, secukinumab, mycophenolate mofetil, adalimumab, methotrexate, etanercept, apremilast, dimethyl fumarate, tofacitinib	Palmoplantar psoriasis, PsO on scalp and elbows, PsA of DIPs and bilateral enthesitis (DAPSA 23)	Complete resolution of palmoplantar PsO, DAPSA 9 (24 weeks)	Recurrent herpes simplex labialis (treated with prophylactic 500 mg valacyclovir QD)
	Zabotti et. Al., 2022	15 mg QD UPA	Case Report	1	rheumatoid arhtritis	Leflunomide, adalimumab biosimilar, methotrexate, systemic	Erythematous plaques with white scaling on b/l LE, legs, and soles	Improvement in RA and clearance of skin lesions (3 months)	None

						steroids, topical steroids			
	Patruno et. Al., 2022	30 mg QD UPA	Case Report	1	atopic dermatitis	Dupilumab, Systemic corticosteroid, topical corticosteroids	Erythematous plaques on scalp, hands, legs	Complete resolution of pruritus, AD, and psoriasiform skin reaction (4 weeks)	None
Palmoplantar Pustulosis	Gaiani et. Al., 2023	15 mg	Case series	3	(1) psoriatic arthritis, (2) plaque psoriasis, osteopenia, multiple fractures (3 Hashimoto's thyroiditis, Vitiligo, fibroids, fibromyalgia, plantar fasciitis	(1) Systemic corticosteroids, acitretin, cyclosporin, methotrexate, apremilast, ustekinumab, ixekizumab, brodalumab (2)Systemic Corticosteroids, acitretin, methotrexate, secukinumab (3) Systemic corticosteroids, cyclosporin, secukinumab, methotrexate	(1) PPGA 3, i-NRS 6 (2) PPGA 4, itch NRS 8 (3) PPGA 3, itch NRS 10	(1) PPGA 0, i-NRS 0 (12 weeks); (2) PPGA 1, i-NRS 1 (7 months); (3) PPGA 1, i-NRS 1 (4 months)	None
	Kooybaran et. Al., 2023	15 mg	Case Series	5	(1) Achilles tendinitis, diabetes, type 2 arterial hypertension,	(1)Fumaric acid esther, methotrexate, apremilast, acitretin,	(1) PPPASI 18.6 (before therapy) PPPASI 3.6,	(1) Stable PPPASI 3.0, PASI 0 (2)PPPASI 1.8 (6	(1) headaches; (3) bronchitis, cystitis

					steatosis hepatitis, hyperlipidemia, hyperthyroidism (2) nail psoriasis, psoriatic arthritis, arterial hypertension, alopecia areata (3) chronic spontaneous urticaria, chronic bronchitis, dyslipidemia (4) psoriatic arthritis, COPD, fibromyalgia, IBD (5) fibromyalgia, arterial hypertension, depression, effluvium, psoriatic arthritis	ustekinumab, brodalumab, guselkumab, adalimumab, anakinra, ixekizumab, tofacitinib (2)Adalimumab, methotrexate, ixekizumab, acitretin, guselkumab (3) Methotrexate, dimethyl fumarate, acitretin, cyclosporine, apremilast (4) Methotrexate, guselkumab (5) Methotrexate, secukinumab, acitretin	PASI 0 (12 months of tofacitinib and methotrexate) (2) PPPASI 19.2 (3) PPPASI 10.5 (4) PPPASI 4.8 (5) PPPASI 9.6	weeks), nail psoriasis and PSA improved (3)PPPASI 4.0 (nine weeks), CSU improved and omalizumab was discontinued (4) PPPASI 0.6 (6 weeks), improved joint pain but morning stiffness persisted (5) PPPASI 6.0 (3 months)	

	Mohr et. Al., 2023	15 mg QD UPA	Case Report	1	psoriasis, hypothyroidism, hypercholesterolemia	Topical psoralen therapy, fumaric acid esters, methotrexate, acitretin, alitretinoin, guselkumab, apremilast	PPPASI 17.7, PASI 1.6, itch NRS 8/10, pain NRS 7/10	PPPASI 3.6 (3 weeks); PPPASI 4.2, PASI 0 (15 weeks), i-NRS 5/10, pain NRS 0/10	Mild perioral dermatitis attributed to masks
Hidradenitis Suppurativa	Kozera et. Al., 2022	15 mg QD UPA and was increased to 30 mg if not showing clinical response	Retrospective Cohort Study	20	N/A	N/A	N/A	HiSCR 75 19/20 (week 12)	1/20 Varicella Zoster infection, 2/20 mild transient transaminitis,16/20 elevated CK w/o no symptoms, 4/20 Covid infections
	Kimball et. Al., 2023	30 mg QD UPA	Clinical Trial	47	N/A	12/35 Anti-TNF blockers	N/A	38.3% achieved HiSCR >50% (week 12)	Prostate Cancer (One patient), urinary tract infection (6 events), headache (7 events), acne (5

									events), cellulitis (1 event)
	Rached et. Al., 2023	30 mg QD UPA	Clinical Letter	1	Crohn's disease	Antibiotics, systemic corticosteroids, adalimumab, infliximab, anakinra, ustekinumab, certolizumab pegol	Generalized eruption of erythematous patches with papules and vesicles with oral yellowish crusts	UPA was discontinued after 5 weeks	VZV infection leading to encephalitis, pneumonia with superinfection, secondary haemophagocytic lymphohistiocytosis
Erythema Multiforme	Murphy et. Al., 2021	15 mg QD UPA + spironolactone	Retrospective Case Series	1/4		Prednisone, rituximab, IVIG, cyclosporine, famciclovir, thalidomide, apremilast, infliximab, spironolactone, tofacitinib	N/A	Almost clear with treatment	None
	Lee et. Al., 2023	15 mg QD UPA	Case Report	1	herpes labialis, endometriosis	Systemic steroids, hydroxychloroquine, famciclovir, cyclosporine,	Multiple erythematous target-like lesions on trunk and extremities	Skin clear with post-inflammatory hyperpigmentation	None

						dapsone, mycophenolate mofetil			
	Deutsch et. Al., 2023	15 mg QD UPA + 15 mg prednisone QD	Case Report	1	grade 3 follicular lymphoma	Topical tacrolimus, Systemic steroids, mycophenolate mofetil, IVIG	Multiple target-like lesions on trunk, acral areas, proximal extremities with labial and oral ulcers	Almost clear with treatment (9 weeks)	Pulmonary infection
Granuloma Annulare	Slater et. Al., 2023		Case Report	1	type 2 diabetes, hypothyroidism, kidney disease	Clotrimazole cream, triamcinolone cream, NBUVB, clobetasol, rifampin, ofloxacin, minocycline, intralesional triamcinolone injections, ruxolitinib cream	Annular plaques with central clearing on bilateral thighs and elbows	Skin is clear of GA (4 months)	None
	Sondermann et. Al., 2022	15 mg QD UPA	Case Report	1	diabetes, obesity, coronary heart disease, RA	None but had treatment resistant PsA	Generalized distribution of annular plaques	Complete resolution (7 days)	None

Lichen Planus	Balestri et. Al., 2022	15 mg QD UPA	Case Report	1	HLA-B27 positive psoriatic arthritis with recurrent anterior uveitis	Multiple treatment for Psoriatic arthritis	Buccal patches of white lacy with an erythematous base	Complete Resolution (7 days)	None
	Kooybaran et. Al., 2021.	15 mg QD UPA	Case Report	1	n/a	Topical corticosteroids, systemic corticosteroids, hydroxychloroquine	Oropharynx pain (7/10) Esophageal pain (9/10)	Oropharynx pain 5/10, Esophageal pain 2/10 (12 weeks); No oral lesions (24 weeks	None
Pyoderma Gangrenosum	Van Eycken et. Al., 2023	15 mg QD UPA + 10 mg prednisone	Case Report	1	HLB-B27 negative spondylarthritis	topical steroids, tacrolimus plus minocycline, systemic corticosteroids, doxycycline, colchicine, azithromycin, prednisone, cyclosporine, secukinumab, apremilast,	painful papulonodular lesions on medial bilateral distal extremities with purulent drainage	Complete remission (12 weeks)	None
	Kooybaran et. Al., 2022	15 mg QD UPA + slow taper of prednisone	Case Report	1	Rheumatoid Arthritis	methotrexate, leflunomide, certolizumab pegol, adalimumab,	Irregularly shaped ulcer with undermined erythematou	PG no longer, ESR and CRP normal, no	None

		lone from 80 mg				prednisolone, anakinra	s borders accompanied by purulent drainage on left foot	pain (14 weeks),	
Pityriasis Rubra Pilaris	Song et. Al., 2023	15 mg UPA	Case Report	1	hypothyroidism, atrial fibrillation, hypertension, aortic valve repair	systemic corticosteroids, dupilumab, acitretin, ixekizumab	Widespread erythroderma except of hands and thighs	<1% BSA at 4 weeks, hair grown back	None
	Saad et al., 2023	30 mg UPA	Case Report	1	None	Topical steroids, calcineurin inhibitors, isotretinoin, phototherapy, ustekinumab, ixekizumab	BSA 80%	BSA 15% (6 weeks)	headache
Vitiligo	Su et. Al., 2023	15 mg QD UPA	Cohort Study	12	N/A	Systemic corticosteroids, calcineurin inhibitors, phototherapy	Average VASI 2.89+3.20	Average 38.65% improvement in VASI	Acne (2 patients)
	Pan et. Al., 2023	15 mg QD UPA	Case Report	1	atopic dermatitis, allergic rhinitis	n/a	VIDA 2, VASI 0.35, EASI-10.5, NRSp 6	Pruritus resolves (24 hours); repigmentation 90% on face, 60% on chest	Acne worsened

								EASI 4.1 (4 months)	
Bullous Pemphigoid	Nash et Al., 2022	15 mg QD UPA	Case Report	1	hypertension, dyslipidemia, osteoarthritis, endometriosis, atopic dermatitis	Prednisone	Urticarial plaques with tense bullae on erythematous plaques	No new blister formation, resolved pruritus, post-inflammatory hyperpigmentation in previous areas of disease (5 months)	None
	Gresham et. Al., 2023	15 mg QD UPA	Case Report	1	Squamous Cell Cancer of Head and Neck managed by immunotherapy, PD-L1 positive tumor metastatic to cervical lymph nodes, malignant melanoma syndrome	ILT4 inhibitor (MK-4830) in combination with pembrolizumab, prednisone, topical corticosteroid	Tense bullae overlaying erythematous patches and urticarial plaques and papules	Improvement in urticaria, decrease in active bullae with increased hemorrhagic crust from previous bullae	Death (2 months) due to metastatic disease
Chronic Prurigo	Gil-Lianes	15 mg QD UPA	Case Series	3	(1) hypertension	Topical and intralesional	(1) PP-NRS 9,	PP-NRS 0 (1 week);	None

	et. Al., 2023				(2) hyperuricemia, allergic rhinitis, contact hand dermatitis, genital lichen sclerosis (3) asthma, hand contact dermatitis, hypercholesterolemia, anxiety, atopic dermatitis	corticosteroids, pregabalin, methotrexate, Topical corticosteroids, antihistamines, Topical and systemic corticosteroids, antihistamines, cyclosporine	DLQI 25 (2) PP-NRS 8, DLQI 22 (3) PP-NRS 9, DLQI 24	Cutaneous lesions (1 month), PP-NRS 0 (1 week); Cutaneous lesions (1 month), PP-NRS 0 (1 week); Cutaneous lesions (2 months)	
	Muntaner-Virgili et. Al., 2023	30 mg QD UPA	Case Report	1	eczematous dermatitis	Intralesional depot triamcinolone injections, topical corticosteroids, cyclosporine, oral corticosteroids, oral corticosteroids, methotrexate, dupilumab	Worse I-NRS 2, IGA 3, generalized hyperkeratotic and pruritic nodules	BSA 0%, Worse i-NRS 0, IGA 0; one nodule left and PIH in previous areas (week 16)	None
Pemphigus foliaceus	Guenin et Al., 2023	15 mg QD (1 week) then 30	Case Report	1	None	Topical corticosteroids, prednisone	Generalized erythematous patches with	Post-inflammatory hyperpigme	None

		mg QD UPA					desquamated bullae and erosions	ntation (week 13 of UPA)	
Lichen Amyloidosis	Solimani et Al., 2023	30 mg QD UPA	Case Report	1	None	Topical steroids, narrow band UVB, acitretin	DLQI 26, i-NRS 9/10	Significant improvement of itch and pain, reduction, reduced epidermal thickness	None
Netherton Syndrome	Li et. Al., 2023	15 mg QD UPA	Case Report	1	eczema, psoriasis, allergic rhinitis	Multiple topical treatments, secukinumab, dupilumab	53% BSA involvement	BSA 29% (1 month); BSA 48% (3 month)	None
Chronic Pruritus	Wachuku et. Al., 2023	15 mg QD UPA	Case Report	1	polycythemia vera, essential thrombocytopenia, atopic dermatitis	Antihistamines, topical steroids, antidepressants, OTC lotions, gabapentin, dupilumab, phototherapy	iNRS 6/10	iNRS 6/10	Painful acneiform lesions
Erythrodermic mycosis fungoides	Castillo et. Al., 2022	15 mg QD UPA	Case Report	1	eczematous dermatitis	Cyclosporine, methotrexate, dupilumab, acitretin, narrowband UV-B therapy	Diffuse generalized erythema with patches of scale (BSA>80%), palpable inguinal lymph node	BSA <10%, improved pruritus (16 weeks)	None

Hailey-Hailey Disease	Murphy et. Al., 2023	15 mg QD UPA	Case Report	1	hypertension, hyperlipidemia, depression, and a family history of a similar condition	Triamcinolone, topical gentamicin, calcipotriene, minocycline, fluconazole, acitretin, dapsone, dupilumab, naltrexone, cyclosporine, prednisone	Erythematous plaques with erosion in skin fold regions (underneath breasts, axilla), thigh, and lower back	Patches of post-inflammatory hyperpigmentation (4 weeks), Completely clear (16 weeks)	None
Acne keloides nuchae	Caudrelier et. Al., 2023	15 mg QD UPA for 6 months + 30 mg QD UPA	Case Report	1	atopic dermatitis	Topical clindamycin, fusidic acid, clobetasol, betamethasone and siacyclic acid, intralesional triamcinolone, minocycline, doxycycline, methotrexate, dupilumab	Annular plaque with multiple erythematous-pinkish papules and pustules with crust on occipital and nuchal scalp	Decreased erythema looking like surrounding skin, decreased papules, and decreased crust around border (10 months)	None
Epidermolysis Bullosa Pruriginosa	Kim et Al., 2023	15 mg QD UPA	Case Report	1	N/A	Cyclosporine, oral steroids	i-NRS 8, diffuse pinkish plaques with papules and numerous bullae	i-NRS 1, no new bullae (10 weeks)	None

Severity of Alopecia Tool (SALT); Eczema Area and Severity Index (EASI); SALT (SALT score not explicitly stated but estimated from photographs); Pruritus-Numeric Rating Scale (P-NRS); Dermatology Life Quality Index (DLQI); Psoriasis Area and Severity Index (PASI); itch Numbering Rate Scale (i-NRS); Pain-VAS (Visual Analogue Scale); Nail Psoriasis Severity Index (NAPSI); Disease Activity Index for Psoriatic Arthritis (DAPSA);Palmoplantar Pustulosis Area and Severity Index (PPPASI); Palmoplantar Pustulosis Physician Global Assessment (PPPGA); Chronic Spontaneous Urticaria (CSU); Hidradenitis Suppurative Clinical Response (HiSCR); Varicella Zoster Virus (VZV); Body Surface Area (BSA); Vitiligo Area Severity Index (VASI); Vitiligo Disease Activity Score (VIDA); Number Rating Scale of Pruritus (NRSp); Investigator Global Assessment (IGA); Peak Pruritus Numeric Rating Scale (PP-NRS).*